CASO CLÍNICO

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Declaration of ethical aspects

Acknowledgement of authorship: The author declares that he/she has contributed to the idea, study design, data collection, data analysis and interpretation, critical review of the intellectual content, and final approval of the manuscript we are submitting.

Ethical responsibilities: Protection of persons. The author declares that the procedures followed conformed to the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Declaration of Helsinki.

Confidentiality of data: The author declares that he has followed the protocols of the Hospital Central de Maracaibo on the publication of patient data.

Right to privacy and informed consent: The author has obtained the informed consent of the patient and/or subject referred to in the article. This document is in the possession of the corresponding author.

Financing: The author certifies that he/she has not received financial support, equipment, personnel or in-kind support from individuals, public and/or private institutions for the conduct of the study.

Received: 26 March 2023

Accepted: 4 July 2023

Online publication:

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Cite as: Reyna-Villasmil E. Acute dengue encephalitis during pregnancy. Rev peru ginecol obstet. 2023;69(3). DOI: https://doi.org/10.31403/rpgo.v69i2559

Acute dengue encephalitis during pregnancy

Encefalitis aguda por dengue durante el embarazo

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DOI: https://doi.org/10.31403/rpgo.v69i2559

ABSTRACT

Dengue is a public health problem. Most patients develop clinical signs ranging from mild illness to hemorrhagic syndrome. Unusual neurological manifestations are rare and there is increasing evidence of neurotropism by the virus. Dengue encephalitis is the result of the multisystem disorder that occurs in severe infection and during pregnancy can be difficult to diagnose. In addition, it is important to consider it as a differential diagnosis in patients in endemic areas in patients with acute febrile illness and neurological symptoms. The management of dengue encephalitis during pregnancy is a challenge and it is necessary to perform all possible tests to decide the optimal and accurate management to avoid maternal complications. A case of acute dengue encephalitis during pregnancy is presented.

Key words: Dengue, Encephalitis, Encephalopathy, Pregnancy

RESUMEN

El dengue es un problema de salud pública. La mayoría de los pacientes desarrollan signos clínicos que van desde enfermedad leve hasta síndrome hemorrágico. Las manifestaciones neurológicas inusuales son raras y cada vez existen más pruebas de neurotropismo. La encefalitis por dengue es el resultado del trastorno multisistémico que ocurre en la infección grave y durante el embarazo puede ser difícil de diagnosticar. Además, es importante considerarla como diagnóstico diferencial en pacientes en zonas endémicas en pacientes con enfermedad febril aguda y síntomas neurológicos. El manejo de la encefalitis por dengue durante el embarazo es un desafío y es necesario realizar todas las pruebas posibles para decidir el manejo óptimo y preciso para evitar complicaciones maternas. Se presenta un caso de encefalitis aguda por dengue durante el embarazo.

Palabras clave. Dengue, Encefalitis, Encefalopatía, Embarazo

Introduction

Dengue virus is a flavivirus that causes a febrile illness transmitted by the *Aedes aegypti* mosquito infected with four closely related but antigenically distinct serotypes. Incidence has increased 30-fold over the past 50 years as a result of increasing geographic spread, with more than 2.5 billion people residing in dengue-endemic countries. An estimated 390 million dengue infections and more than 90 million apparent illnesses occur each year[1,2]. The infection is self-limiting with a spectrum ranging from uncomplicated febrile illness to hemorrhagic manifestations and refractory shock[3].

The virus can affect any part of the nervous system, including the peripheral nervous system and ophthalmic structures, due to its neurotropic nature[4,5]. Neurological complications include encephalopathy, encephalitis, acute disseminated encephalomyelitis, transverse myelitis, Guillain-Barre syndrome, myositis and optic neuritis[4]. Dengue encephalitis during pregnancy presents nonspecific symptomatology, leading to diagnostic delay, especially when the clinical picture is similar to that observed in pregnancy-induced hypertension. In these cases, clinical suspicion is necessary for diagnosis and specific management[6]. A case of acute dengue encephalitis during pregnancy is presented.

Case report

A 32-year-old female patient, III gestations, II paras, 28 weeks pregnant, was brought to the emergency room for presenting generalized tonic-clonic seizures accompanied by headache, drowsiness and fever that started three days before the seizure. Family members denied a history of vomiting, petechiae, bleeding, smoking and use of illicit substances. The patient lived in an area declared endemic for dengue fever.

Physical examination showed temperature of 39.5°C, blood pressure of 160/105 mmHg, heart rate of 115 beats per minute, Glasgow scale of 9/15 points (eye opening = 2, verbal response = 2, motor response = 5), hyperreflexia, bilateral Babinski's sign and positive clonus. Kernigs and Brudzinki signs were negative, with intact cranial nerve functions. Pupils were of adequate size with normal reaction to light and fundoscopy was normal. Both pyramidal and extrapyramidal signs were absent. Mental status evaluation found the patient to be irritable and, although she could obey commands and answer questions appropriately, her responses appeared confused. No rash, bleeding, cervical lymphadenopathy, hepatosplenomegaly, cervical stiffness, joint pain, cough, dyspnea, or chest pain were noted. The abdomen was soft and depressible with enlarged uterus with single fetus in transverse position, active fetal movements, fetal heart rate present and no evidence of contractile activity. Vaginal examination showed no alterations.

Initial laboratory tests revealed hemoglobin 11.6 g/dL, hematocrit 36.3%, leukocytes 5,180/mL (neutrophils 62% and lymphocytes 17%) and platelet count 110,000/mL. Peripheral blood smear showed thrombocytopenia consistent with possible viral infection, without evidence of microangiopathic hemolytic anemia. Electrolytes, coagulation profile, liver and renal function tests were within normal limits. Urine examination showed only trace protein without evidence of hematuria.

The patient was initially treated with intravenous benzodiazepine as initial anticonvulsant and then intravenous magnesium sulfate plus sublingual nifedipine, without improvement of the clinical picture. Evaluation by the neurology service was requested, which suggested performing a lumbar puncture. Evaluation of the cerebrospinal fluid (CSF) showed it to be clear, colorless, and acellular. Gram and acid-fast bacilli stains were negative. Glucose values were 66 mg/dL (considered low when compared to glycemia 81 mg/dL), protein 105 mg/dL and chloride 115 mg/dL. Tests for venereal disease, cytomegalovirus, toxoplasmosis, and rubella were negative. Blood, CSF, and urine cultures showed no growths of microorganisms. Brain magnetic resonance imaging revealed nonspecific focal changes without evidence of hemorrhage. Prenatal ultrasound showed a single male fetus in accordance with gestational age, without obvious macroscopic alterations and with normal amniotic fluid volume.

The patient was transferred to the intensive care unit with careful fluid management, regular fetal monitoring and different measures to avoid bleeding. Blood tests for malaria, as well as IgM and IgG for dengue, were negative. However, the non-structural antigen 1 (NS-1) protein test for dengue was positive. The clinical presentation together with the imaging findings and laboratory test results allowed a diagnosis of acute dengue encephalitis to be made. Fever began to decrease on the fourth day, and clinical improvement was observed with no seizures or bleeding episodes during her stay. After 12 days, the patient was transferred to hospitalization and subsequently discharged with follow-up by prenatal consultation.

Discussion

Dengue virus belongs to the *Flaviviridae* family which also includes yellow fever, Japanese encephalitis, and West Nile viruses. The virus infects cells of the immune system, especially macrophages and monocytes, so the host immune response is crucial in the pathogenesis of the disease[7]. Neurological manifestations are rare in patients with dengue. Initially the virus was considered to be non-neurotropic[8]. However, although initially there was uncertainty about dengue encephalitis as an entity, the virus has neuroinvasive potential. The presence of the virus and IgM antibodies in CSF has been demonstrated in patients with neurological manifestations[6,9]. Among the four serotypes, types 2 and 3 are the most likely to produce neurological complications[10]. Encephalitis is the most common neurological manifestation and its incidence ranges from 0.5%-6%[5].

In the acute phase of dengue infection, shock syndrome, cerebral edema and anoxia, metabolic acidosis, electrolyte disturbances, vasculitis, hepatic and renal failure may lead to the development of encephalopathy. The symptomatology of dengue encephalitis is secondary to autoimmune reactions in the cerebral white matter secondary to the transient compromise of the blood-brain barrier[11]. Vasculitis with fluid extravasation also has some role in the pathophysiology[12]. Only half of the cases of encephalitis present classic dengue symptoms (myalgias, diarrhea, abdominal pain, arthralgias, skin rash and/or hemorrhage) caused by cytokine and complement activation, endothelial and platelet dysfunction and consumption coagulopathy[11].

The symptoms of dengue encephalitis are diverse and are related to the location of the lesion in the central nervous system. These include headache, irritability, insomnia, sensory disturbances and seizures in the absence of intracranial hemorrhage. These are self-limited and generally do not produce sequelae. Generally, the neurological picture appears early in the course of the infection (even on the first day of the disease) and coincides with the viremic phase, although in most cases it appears between 2-30 days after the onset of the febrile picture[10]. Other neurological manifestations such as motor deficits may occur during acute infection (myelitis and myositis) or during the post-dengue stage (polyradiculoneuritis, encephalomyelitis, neuromyelitis optica, polyneuropathy and mononeuropathy) [13,14]. Diagnosis during pregnancy can be difficult, so the physiological changes of pregnancy, pregnancy-related complications, and other medical conditions should be considered along with laboratory findings.

The proposed diagnostic criteria for dengue encephalitis are fever, acute signs of brain involvement associated with the presence of dengue IgM or RNA in serum and/or CSF, in addition to the exclusion of other possible causes of encephalitis and viral encephalopathy. Antibody detection is the most commonly used technique for diagnosis, as it has high sensitivity and specificity. The detection of NS1 can also be used for early diagnostic purposes, as it is present at the onset of the first symptoms and can persist for up to 14 days[12].

The results of conventional laboratory tests (hemoconcentration, thrombocytopenia) in patients diagnosed with dengue encephalitis are nonspecific. Subtle neurological changes may be observed in the absence of significant hemoconcentration and thrombocytopenia[10]. For example, hematocrit values during pregnancy are close to 33% (the normal value in non-pregnant women is around 38%)[15]. As there is a physiological increase in intravascular volume during pregnancy, the identification of hemoconcentration, thrombocytopenia or hypoproteinemia may not be very useful, which may lead to an underestimation of the frequency of complications during pregnancy. In addition, pregnant women are at increased risk of maternal-fetal hemorrhage, preeclampsia, spontaneous abortion, fetal anomalies, low birth weight, preterm delivery, cesarean section, and maternal-fetal mortality[16]. Routine complementary hematology, biochemistry and liver function tests plus tests for rheumatic diseases, hepatitis and human immunodeficiency virus should be performed in all suspected patients to monitor and better understand the disease[12].

To confirm the diagnosis of dengue encephalitis, it is necessary to take CSF samples. Test results may be normal, which does not exclude the diagnostic possibility, as up to 50% of cases may have normal results[10]. The analysis should include cell count, protein and glucose/lactate determination, smear and culture for bacteria-fungi. Also useful is the evaluation of blood-brain barrier function by albumin ratio (CSF/serum), determination of specific antibodies against syphilis, cytomegalovirus, Epstein-Barr, and herpes simplex. With regard to specific tests for dengue, specific antibodies, NS1, RNA or viral antigen should also be determined. These results can be useful to rule out other pathologies[5].

Although laboratory tests represent the definitive diagnostic tool, brain imaging studies add information on the possible etiology of encephalitis. MRI is the ideal diagnostic modality in patients with dengue encephalitis, as it provides better definition of brain structures, although it is unable to establish the cause of encephalitis. Images usually show cerebral edema, white matter changes, necrosis and cerebral atrophy[7]. Hyperintense and focal areas in the temporal lobes, thalamus, hippocampus, pons and spinal cord

may also be seen. However, these findings are not pathognomonic of dengue encephalitis[17].

Differential diagnoses of dengue encephalitis during pregnancy include idiopathic thrombocytopenic purpura complicated with intracranial hemorrhage, systemic lupus erythematosus with cerebral vasculitis, antiphospholipid antibody syndrome with central nervous system involvement and pregnancy complications such as preeclampsia, hemolysis syndrome, elevated liver enzymes and thrombocytopenia (HELLP syndrome), thrombotic thrombocytopenic purpura, sepsis and disseminated intravascular coagulation[6].

General management of viral encephalitis includes airway monitoring and maintenance, oxygenation, hydration, and adequate nutrition. Treatment of dengue encephalitis is supportive and includes careful monitoring, replacement of intravascular fluid and electrolyte losses, and seizure control. Both monitoring of the clinical condition and serial determination of hematocrit and platelet values are essential to prevent complications, which can be treated with plasma expanders and/or blood products[5]. There is no specific antiviral treatment for dengue[10]. However, some cases with persistent neurological symptoms can be treated with glucocorticoids, which highlights the importance of early diagnosis to improve prognosis[9]. Reported mortality is low and most patients recover without sequelae.

In conclusion, dengue is a major public health problem worldwide, especially in endemic countries. Dengue encephalitis is a rare but recognized manifestation that can complicate pregnancy. It may appear early in the course of the disease with manifestations undifferentiated to other viral causes with normal blood counts. Knowledge of the various neurological complications associated with dengue infection can help identify the underlying pathologic processes and make the correct diagnosis, allowing for appropriate treatment and improved prognosis.

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